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CRITICAL REVIEW

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Pharmaceuticals and personal care products in effluent matrices: A survey of transformation and removal during wastewater treatment and implications for wastewater management

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Pharmaceuticals and personal care products in effluent matrices: A survey of transformation and removal during wastewater treatment and implications for wastewater management†‡

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Pharmaceuticals and personal care products (PPCPs) represent pollutants of emerging concern, originating in surface and drinking waters largely from their persistence in wastewater effluent. Accordingly, a wealth of recent investigations has examined PPCP fate during wastewater treatment, focusing on their removal during conventional (*e.g.*, activated sludge) and advanced (*e.g.*, ozonation and membrane filtration) treatment processes. Here, we compile nearly 1500 data points from over 40 published sources pertaining to influent and effluent PPCP concentrations measured at pilot- and full-scale wastewater treatment facilities to identify the most effective series of technologies for minimizing effluent PPCP levels. Available data suggest that at best a 1-$\log_{10}$ concentration unit (90%) of PPCP removal can be achieved at plants employing only primary and secondary treatment, a performance trend that is maintained over the range of reported PPCP influent concentrations (*ca.* 0.1–10^5 ng L^{-1}). Relatively few compounds (15 of 140 PPCPs considered) are consistently removed beyond this threshold at facilities using solids removal and conventional activated sludge (CAS), and most PPCPs are removed to a far lesser extent. Further, increases in CAS hydraulic retention time or sludge retention time do not appreciably increase removal beyond this limit. In contrast, plants employing advanced treatment methodologies, particularly ozonation and/or membranes, remove the vast majority of PPCPs beyond 1-$\log_{10}$ concentration unit and oftentimes to levels below analytical detection limits in effluent. Data also indicate that passive approaches for tertiary treatment (*e.g.*, wetlands and lagoons) represent promising options for PPCP removal. We conclude by addressing future challenges and frontiers in wastewater management posed by PPCPs including analytical needs for their real-time measurement, energy demands associated with advanced treatment technologies, and byproducts arising from transformation of PPCPs during treatment.

I. Introduction

Over the past decade, overwhelming evidence has shown that pharmaceuticals and personal care products (PPCPs) are ubiquitous in surface water, groundwater, and even some drinking waters.[1–3] Improved analytical methodologies have lowered detection limits for these compounds to parts per trillion (ppt) levels even in the most complex of environmental matrices, leaving little doubt as to their occurrence in water supplies around the globe. What remains, however, is a growing list of questions pertaining to the environmental fate of PPCPs, the ecotoxicological and human health risks associated with their

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Environmental Impact

This review examines the fate of pharmaceuticals and personal care products (PPCPs) during wastewater treatment and their occurrence in effluent matrices. We use trends in published data for influent and effluent PPCP concentrations measured at wastewater treatment facilities to critically evaluate the current ability of wastewater infrastructure to deal with this emerging pollutant class. As outcomes of this review, we identify best-case scenarios for PPCP removal over a range of treatment technologies and configurations, and identify those PPCPs most recalcitrant to traditional treatment methodologies. These findings should help to focus future ecotoxicological studies on species with the highest probability of being encountered at appreciable levels in surface waters due to effluent discharge. Further, recommendations on alternative treatments that can be used to minimize effluent PPCP loads will help to establish best practices for wastewater management in the event standards regulating PPCP removal are adopted.

occurrence, and the ability of current water and wastewater treatment infrastructure to effectively remove these compounds.

The dominant route for PPCP entry into the environment is through effluent from domestic wastewater treatment. Accordingly, PPCPs and their metabolites are often referred to as "effluent-derived" contaminants,[4] originally present in wastewater from their use in medicinal and personal care products and ultimately discharged into municipal sewer systems as human waste products. The tendency for these compounds to persist or be only partially degraded during treatment or to bypass treatment altogether *via* sewage overflows will, therefore, contribute to their load in receiving waters, many of which serve as recreational and drinking water sources.

Concerns over the biological activity of PPCPs, specifically their potential to act as endocrine disruptors,[5] have motivated laboratory, pilot- and full-scale investigations exploring their occurrence in treatment plant influent, their removal during unit operations and processes utilized in wastewater treatment, and the concentrations that persist in treated effluent. Despite over a decade of study, however, consensus on many of these issues remains limited. This is due in part to the large number of PPCPs available commercially and through prescription, the diverse chemical structure and physicochemical properties common PPCPs display, and the range of unit operations and operating conditions employed during wastewater treatment.

This review uses published data pertaining to the occurrence of PPCPs in wastewater influent and effluent to evaluate treatment plant performance in removing this emerging contaminant class. We aim to identify those compounds most likely to persist during wastewater treatment and, therefore, pose the greatest probability of exposure after effluent discharge. Removal efficiencies implied from differences in influent and effluent concentration data are also rationalized on the basis of results from laboratory, pilot-scale and full-scale studies examining the fundamental mechanisms of PPCP removal in specific unit operations and processes employed in wastewater treatment, including traditional (*e.g.*, solids removal and biological wastewater treatment), advanced (*e.g.*, membranes and advanced oxidation processes), and passive or natural (*e.g.*, lagoons and wetlands) treatment approaches.

Although PPCPs are not routinely monitored in wastewater treatment, nor is their occurrence in effluent regulated, public perception and concerns over possible adverse health and ecosystem effects associated with exposure to PPCPs and PPCP mixtures have resulted in increased scrutiny of their fate during wastewater treatment. It can be argued, therefore, that wastewater engineers should strive to implement treatment approaches that not only focus on traditional targets such as suspended solids, biochemical oxygen demand (BOD) and nutrients, but

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also efficiently and cost-effectively reduce PPCPs levels in treated effluent. Accordingly, we draw upon the available literature to develop recommendations for optimal technologies for lowering PPCP loads in effluent. Finally, we conclude by identifying future frontiers and challenges associated with PPCPs in wastewater, while also addressing the implications and potential hurdles that PPCPs pose to wastewater management.

We note that we do not address analysis of PPCPs, but refer the reader to outstanding reviews on this topic,[6–13] as well as recent special issues devoted to PPCPs in *Trends in Analytical Chemistry* (June 2007) and *Analytical and Bioanalytical Chemistry* (February 2007).

II. PPCP occurrence and removal during wastewater treatment: An analysis of the current literature

To better predict the occurrence and concentrations of PPCPs in wastewater effluent, a thorough understanding of their removal during wastewater treatment is warranted. Wastewater treatment involves a series of physical, chemical and biological unit operations and processes that are broadly designated as primary, secondary or tertiary treatment. Primary treatment encompasses solids removal through the sequential processes of coagulation, flocculation and sedimentation. Secondary or biological treatment is intended to reduce the organic load or BOD of the influent *via* approaches including activated sludge, trickling filters and membrane bioreactors (MBRs). In this review, the term tertiary treatment will be applied to all additional steps beyond primary and secondary operations. These encompass operations that are physical (*e.g.*, filtration, adsorption), chemical (*e.g.*, chemical oxidation, disinfection) or biological (*e.g.*, nutrient removal, wetlands and lagoons) in nature.

A growing number of studies have evaluated PPCP fate at full-scale wastewater treatment facilities, and their results are a valuable tool for evaluating PPCP occurrence in wastewater effluent. Thus, we compiled PPCP influent and effluent concentration data from over 40 published sources, which surveyed the performance of more than 100 pilot- and full-scale wastewater treatment facilities or treatment configurations from around the globe. This effort produced a database (provided in the ESI‡) of nearly 140 compounds and 1500 data points related to site-specific PPCP concentrations in the influents of treatment plants and effluents of specific treatment processes. Analysis was limited to pharmaceuticals, and, to a lesser degree, some personal care products. The plants surveyed utilized traditional wastewater treatment (*i.e.*, solids removal with biological treatment *via* activated sludge) as well as more advanced approaches including MBRs, sand filtration, ultra-, micro-, and nanofiltration, reverse osmosis, activated carbon, and chemical oxidation *via* ozonation.

This survey is not meant to be an exhaustive review of all occurrence studies for PPCPs during wastewater treatment. Rather, it is intended to serve as a representative database of typical influent and effluent concentration data that can be used to assess current performance of wastewater treatment plants (WWTPs) for PPCP removal. Our analysis is limited to studies reporting corresponding influent and effluent concentrations for the same WWTP. Unless noted, studies reporting only influent or effluent concentrations or studies that only provide inlet and outlet concentrations for a specific treatment process were not included because they provide no insight as to the total degree of PPCP removal within the facility (*i.e.*, the difference in concentration between raw influent and final treated effluent).

There are some limitations to this analysis, which draws data from a broad range of independent sources. First, we only report compounds quantifiable in both the influent and effluent at the same WWTP. When values below the effluent detection limit were reported, the method detect limit (MDL) was used for comparison to the corresponding influent concentration. These instances have been noted. Second, we do not differentiate between various sampling approaches (*e.g.*, grab *versus* 24 h composite), nor do we rigorously account for variations in the operational parameters (*e.g.*, hydraulic residence time, sludge loading, *etc.*) at each facility. For studies reporting replicate concentrations from one sampling event or concentrations from multiple sampling events temporally close to one another, the mean concentration was used in our analysis. However, for studies in which multiple sampling events occurred at a single facility over an extended time period, data from each sampling event rather than the mean of all events were used to account for possible seasonal variations in PPCP loads.

A. PPCP removal during conventional (primary and secondary) wastewater treatment

Studies of PPCP fate during primary wastewater treatment (*i.e.*, coagulation, flocculation and sedimentation) are generally limited[14–18] because results from drinking water treatment often suggest that removal during these stages is relatively insignificant. In contrast, the greatest contribution to PPCP removal during conventional wastewater treatment occurs during secondary (*i.e.*, biological) treatment.[19] It is, therefore, the most thoroughly studied process with respect to PPCP removal, and a multitude of data exist pertaining to treatment efficiency. We note that for ease of comprehension, the term "removal" will be used to describe not only processes that result in true removal of PPCPs from the treatment stream (*e.g.*, adsorption onto sludge or solids) but also those that lead to PPCP transformation (*e.g.*, biodegradation or chemical reaction), even though the latter do not constitute true removal because metabolites and transformation products will remain in the system.

The most detailed work on PPCP removal during primary treatment has been conducted by Carbella and co-workers.[14,15] They examined the fate of several PPCPs during solids removal in a WWTP in Spain,[14] and in a subsequent work conducted laboratory experiments to examine the influence of coagulant identity and loading, temperature, and mixing time on PPCP removal from WWTP influent.[15] As expected, their findings suggest that PPCP removal at this stage is generally limited, only occurring to a significant extent (>20%) for very hydrophobic compounds such as musks (*i.e.*, galaxolide and tonalide), which exhibit high octanol-water partitioning coefficients (log $K_{ow} \sim 5.5$–6.0). Accordingly, it is widely believed that the predominant PPCP removal mechanism is sorption to suspended organic matter that is subsequently removed *via* coagulation, flocculation and sedimentation. As such, descriptors of PPCP organic partitioning such as K_{ow} values or solid-water distribution coefficients (K_d values) are often suggested as predictors of

PPCP removal, although insufficient data from primary treatment facilities exist to validate such correlations.

Conventional activated sludge (CAS) is the most common biological treatment system used in wastewater treatment. PPCP removal during CAS treatment can be attributed to both biodegradation and adsorption of the compounds to the sludge. Adsorption to sludge is particularly important for compounds with $K_d$values greater than 300 kg L^{-1}.[20] For many acidic PPCPs with low K_d values, removal can be ascribed to biodegradation;[20] this may encompass both metabolic and co-metabolic pathways.[21] In contrast, fragrances such as galaxolide and tonalide are predominantly removed *via* adsorption on sludge.[22]

Fig. 1 shows the extent of PPCP removal in conventional wastewater treatment facilities (*i.e.*, those employing primary treatment and CAS). Data, which pertain to concentrations in the treatment plant influent and CAS effluents, were obtained from published sources[14,23–55] and are presented on a log-log scale. This scale is necessary given the broad range of PPCP concentrations encountered in wastewater treatment, which spans nearly six orders of magnitude (from ~0.1 to 10^5 ng L^{-1}).

Even though some scatter in the data exists, a number of species are essentially resistant to conventional treatment (data located along or above the "no removal" line). A useful point of comparison is effluent levels corresponding to the removal of 1-$\log_{10}$ concentration unit (or 90%) of PPCP. In the U.S., national standards for secondary treatment require an average removal of BOD_5 over a 30-day interval of no less than 85%,[56] or roughly, one-$\log_{10}$ equivalent of removal. Thus, juxtaposition of the influent-effluent data to this unit-$\log_{10}$ removal line (indicated in Fig. 1) allows WWTP performance toward an emerging organic pollutant class (*i.e.*, PPCPs) to be compared to the classical treatment goal for organic removal (*i.e.*, lowering biochemical oxygen demand).

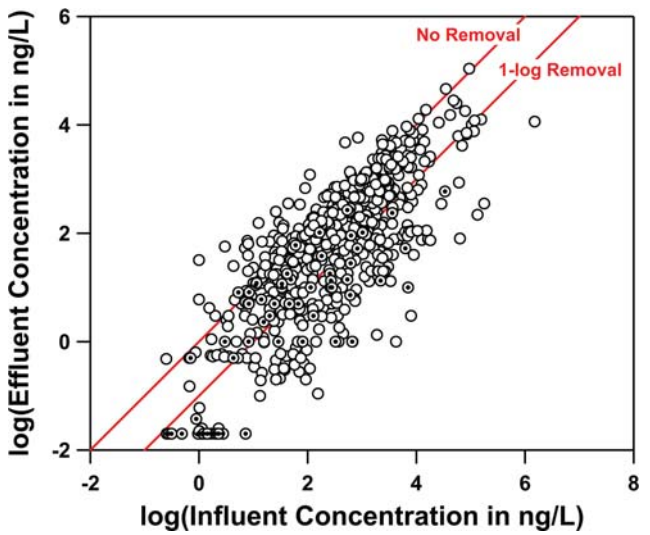


Fig. 1 Comparison plot of PPCP effluent concentration as a function of influent concentration for WWTPs utilizing traditional treatment operations (*i.e.*, solids removal and conventional activated sludge). Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal). Data with center dots indicate instances where effluent PPCP concentrations were below the MDL, in which case effluent data represent the reported MDL. Additional details regarding data compilation are provided in the text.

As shown in Fig. 1, wastewater treatment plants utilizing only solids removal and CAS tend to achieve less than a 1-$\log_{10}$ concentration unit of PPCP removal. Of the 818 (n_{total}) available data points pertaining to PPCP concentrations in conventional treatment plant influents, only 25% ($n_{1\text{-log}}$ = 202) exceeded 1-$\log_{10}$ removal in the corresponding effluent concentrations. Notably, this trend holds over the entire range of PPCP influent concentrations. It can be generally assumed, therefore, that facilities not employing some form of tertiary treatment remove at best 90% of influent PPCPs.

Although ecotoxicological data are lacking to evaluate whether this removal threshold is sufficient for PPCPs, there are instances where only 1-$\log_{10}$ removal may be cause for concern. For example, a PPCP influent concentration of 10^5 ng L^{-1} (or 100 μg L^{-1}) is likely to yield an effluent level of 10 μg L^{-1}, and laboratory studies have shown concentrations on this order can induce adverse ecotoxicological effects toward aquatic organisms. Specifically, triclosan and ciprofloxacin concentrations as low as 0.012–1.5 μg L^{-1} were found to induce a strong, concentration-dependent decline in genus diversity of algal communities sampled upstream and downstream of a WWTP in Kansas.[57]

As highlighted in a recent review of PPCP biodegradation during wastewater treatment,[58] the available literature does not allow for generalizations to be made regarding the removal of different compound classes or even individual compounds. Indeed, the data presented in Fig. 1 were heavily compound specific. Fig. 2 presents the $\log_{10}$ removal efficiencies reported for select compounds in WWTPs employing solids removal and CAS, illustrating differences in treatment that exist not only between PPCPs but also among WWTPs.

One of the most highly researched PPCPs is ibuprofen, an over-the-counter anti-inflammatory. Our database (see the ESI) contains 65 reports of influent and effluent concentrations from conventional treatment facilities for ibuprofen, with roughly 70% ($n_{1\text{-log}}$ = 44) reporting treatment efficiencies greater than 1-$\log_{10}$ removal (Fig. 2). Other compounds with particularly high susceptibility to conventional treatment are shown in Table 1. These include acetaminophen (or paracetamol), thymol, aspirin, salicylic acid, estriol, 17β-estradiol, estrone, fenoprofen, bezafibrate, bisphenol A, cortisol, cortisone, dexamethasone, and prednisone. This relatively small subset of compounds, including ibuprofen, comprise 160 of the 202 (~80%) instances in the entire dataset exceeding 1-$\log_{10}$ removal. Conventional wastewater treatment may be sufficient for their removal, particularly at low influent concentrations.

In contrast, certain species are essentially recalcitrant to conventional treatment. A good example is the antiepileptic carbamazepine; effluent concentrations from conventional treatment facilities are practically equal to influent concentrations for all 48 reported instances of carbamazepine detection. Other compounds that can generally be considered resistant to primary and secondary treatment are summarized in Table 2. These include diclofenac, iopromide, metoprolol, and sotalol. For these compounds, greater than two thirds of available studies report treatment efficiencies of less than 30% *via* solids removal and CAS. We add that there are likely other PPCPs that fit these criteria, but this subset represents those for which sufficient amounts of full-scale treatability data (5 or more published studies) exist.

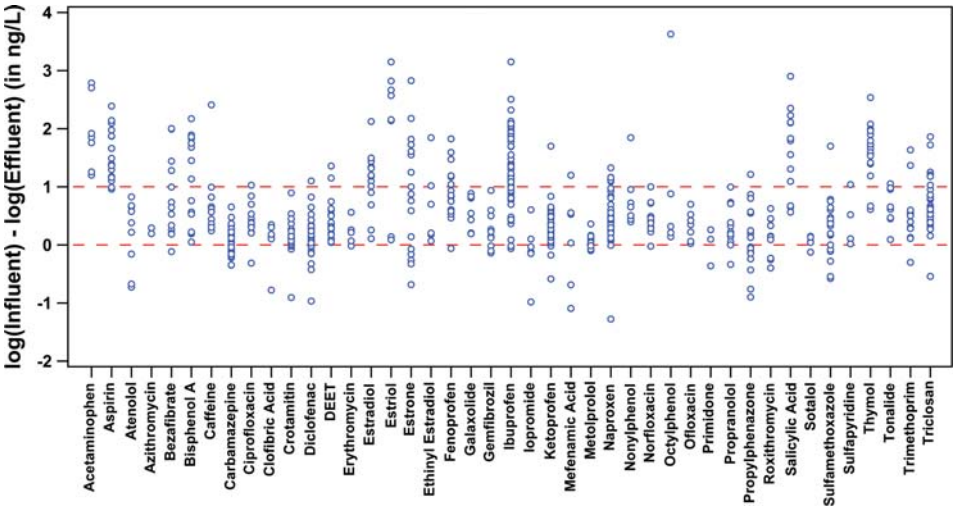


Fig. 2 Log_{10} removal efficiencies for select compounds at WWTPs utilizing traditional wastewater treatment operations (*i.e.*, solids removal and conventional activated sludge). Each data point corresponds to a published report of influent and effluent concentration for a PPCP at a WWTP using these treatment technologies. Dashed lines show thresholds indicating no PPCP removal and removal corresponding to 1-log_{10} concentration unit (90% removal).

Relative to CAS, PPCP removal by trickling filters has received less scrutiny, and there are fewer field-scale occurrence studies at plants using trickling filters. Findings to date generally agree that trickling filters exhibit lower PPCP removal than CAS systems.[18,47,59] Exceptions are endocrine disruptors, which have been found to be more effectively removed *via* trickling filters than CAS.[47] The authors attributed this finding to the ability of trickling filters to produce immobilized, stable bacterial populations that are more capable of degrading recalcitrant compounds, whereas in CAS systems these bacteria are likely to get washed out before stable populations can be established.

PPCP removal by secondary treatment systems still faces several challenges. First, open questions remain regarding the influence of temperature, as well as of operational parameters such as hydraulic retention time (HRT) and solids retention time (SRT) on removal efficiency. As discussed in detail by Onesios *et al.*,[58] several studies have found an enhanced elimination of PPCPs during warmer seasons, whereas at least one study reported no effect of temperature on removal. Opposing conclusions have also been reached regarding the effect of SRT and HRT on treatment performance. For example, Maurer *et al.*[39] reported that the elimination of beta-blockers in WWTPs depended on HRT. In contrast, Joss *et al.*[20] found no impact of either SRT or HRT on the removal of seven pharmaceuticals and fragrances in full-scale WWTPs. Similarly, Göbel *et al.*[60] found no difference in the removal efficiencies of various antibiotics in two WWTPs with SRTs of 21–25 and 10–12 days, respectively. We note that for Figs. 1 and 2, data correspond to CAS systems with reported HRT values ranging from 1 h to as much as 10 days and SRT values spanning 5 h to over 100 days. Clear trends in PPCP removal as a function of these variables could not be discerned in our analysis.

Second, studies of PPCP removal during biological treatment have mainly focused on the original PPCP, whereas much less scrutiny has been devoted to the fate of their metabolites. Several studies[60–62] have found that human metabolites are present in wastewater at higher concentrations than their respective parent compounds. It has also been suggested that some metabolites, in particular glucuronide conjugates, can be transformed back into the parent PPCP during secondary treatment.[43,62,63] These examples highlight the need for future studies to include metabolites when assessing the fate of PPCPs during secondary treatment.

Finally, as previously noted, it is not yet possible to predict the propensity of micropollutants to undergo biodegradation based on their physical-chemical properties (*e.g.*, see the study conducted by Joss *et al.*).[20] This lack of fundamental insight presents one of the biggest challenges in optimizing PPCP removal during secondary treatment. In particular, it is difficult to assess the biodegradation efficiency for new and untested compounds in the absence of analytical measurements or experimental investigation. Yu *et al.*[33] compared biodegradation efficiencies predicted using the software package BIOWIN to PPCP removal measured in full-scale treatment plants and laboratory experiments, finding great discrepancies between predictions and measurements. Instead of *ab initio* predictions, we thus currently rely on empirical data, such as that presented here, to predict biodegradation efficiency during wastewater treatment. As a notable example, Joss *et al.*[64] proposed a simple classification scheme for the biodegradability of pharmaceuticals based on their biodegradation rate constants obtained in batch experiments. Compounds were divided into three classes according to their extent of removal, with the authors ultimately concluding from this scheme that current practices in municipal wastewater treatment do not remove micropollutants efficiently.

B. PPCP removal during advanced wastewater treatment operations

We now compare the efficiency of PPCP removal in conventional wastewater treatment to removal efficiencies reported at facilities employing alternative approaches for secondary treatment (*e.g.*, MBRs) and tertiary treatment operations for secondary effluent (*e.g.*, depth and membrane filtration, chemical oxidation

Table 1 Compounds most susceptible to removal *via* traditional wastewater treatment (*i.e.*, solids removal and conventional activated sludge) based upon data available in studies cited herein. Analysis was limited to compounds with at least five reports of corresponding influent and effluent concentrations.

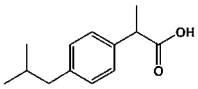
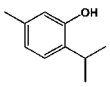
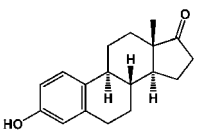
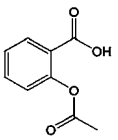
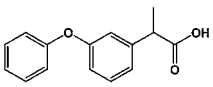
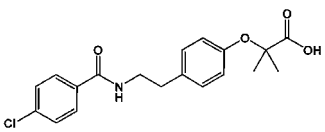
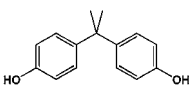
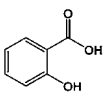
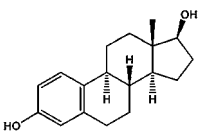
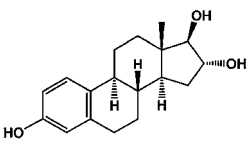
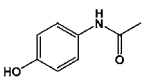
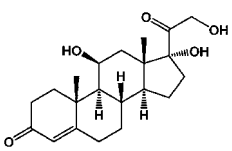
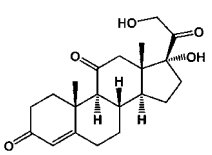
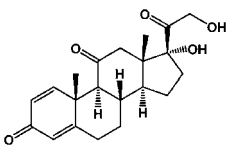
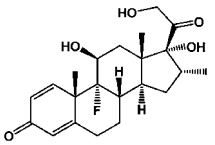
Compound (CAS #)	Chemical Structure	Compound Class	Number of Studies (n)	>1-log Removal (% of Studies)
Ibuprofen (15687-27-1)		Anti-inflammatory	65	44 (69%)
Thymol (89-83-8)		Antimicrobial	18	16 (89%)
Estrone (53-15-7)		Hormone	18	8 (44%)
Aspirin (88566-80-7)		Analgesic	17	16 (94%)
Fenoprofen (29679-588-1)		Anti-inflammatory	17	7 (41%)
Bezafibrate (41859-67-0)		Lipid Regulator	15	5 (33%)
Bisphenol A (80-05-7)		Endocrine Disrupting Compound	14	5 (35%)
Salicylic Acid (69-72-7)		Anti-inflammatory	13	10 (77%)
17β-Estradiol (50-28-2)		Hormone	13	9 (69%)
Estriol (50-27-1)		Hormone	8	6 (75%)
Acetaminophen (8055-08-1)		Analgesic	7	7 (100%)
Cortisol (8056-11-9)		Gluco-corticoid	7	7 (100%)
Cortisone (50-22-6)		Gluco-corticoid	7	7 (100%)

Table 1 (*Contd.*)

Compound (CAS #)	Chemical Structure	Compound Class	Number of Studies (n)	>1-log Removal (% of Studies)
Prednisone (53-03-2)		Gluco-corticoid	7	7 (100%)
Dexamethasone (50-02-2)		Gluco-corticoid	6	6 (100%)

with ozone, and sorption with activated carbon). When available, influent-effluent data for each treatment technology are compared directly to trends observed for conventional wastewater treatment. For this analysis, reported effluent concentrations from each treatment technology are compared to concentrations measured in the plant influent; this allows the extent of PPCP removal achievable *via* a treatment train incorporating each technology to be evaluated. Occasionally, we also present influent-effluent data comparing the removal efficiencies of select PPCPs reported for each technology, thereby helping to identify those approaches most suitable for a particular compound or compound class.

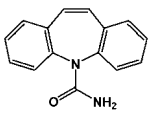
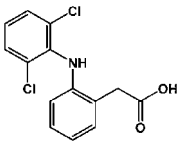
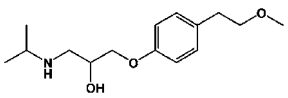
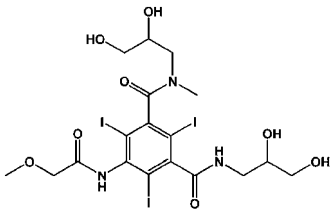
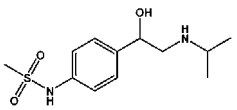
B.1. Membrane bioreactors (MBRs). To enhance biodegradation of PPCPs, MBRs have emerged as an alternative approach to CAS. Like CAS, MBRs rely on biodegradation as the dominant removal mechanism, but their operational parameters, such as HRT, SRT and sludge concentration differ greatly. MBRs operate at higher sludge concentrations that yield increased biological activity compared to CAS. It has therefore been assumed that they will lead to greater PPCP removal, yet studies have reported contradictory findings. Enhanced removal in MBRs has been observed in several studies,[38,65–67] albeit not for all compounds investigated. In contrast, other authors have reported no benefit of MBRs relative to CAS.[20,29,60] A generalization for these contrasting findings was offered by Weiss *et al.*,[68] who concluded that MBRs were only superior for compounds with an intermediate biodegradation potential, whereas no benefits were apparent for easily biodegradable or recalcitrant compounds. The authors therefore questioned whether the use of MBRs was justified because of its limited benefits. In contrast, De Wever *et al.*[69] argued that while MBRs do not necessarily yield higher removal efficiencies, they are nevertheless beneficial because they exhibit a more consistent performance and shorter lag times, indicating a superior response to fluctuating influent concentrations.

Our literature survey suggests that MBRs result in modest improvements in PPCP removal efficiency relative to CAS systems. Fig. 3 compares PPCP concentrations measured in WWTP influents to concentrations measured in the corresponding effluents of MBRs utilized for wastewater treatment.[21,27,29,30,38,39,70,71] Also included are data previously presented in Fig. 1 for conventional wastewater treatment. Using the threshold of 1-$\log_{10}$ removal to compare treatment efficiency, 49% (63 out of 129 data points) of reported PPCP concentrations in MBR effluents exhibit this degree of removal, relative to 25% of PPCP concentrations in CAS effluent.

An alternative means of comparing the performance of PPCP treatment technologies is through percentiles analysis of reported treatment efficiencies. This is shown in Fig. 4, where the box plot illustrates the distribution of reported removal efficiencies, expressed as the fraction of PPCP remaining in the treated effluent, for CAS, MBRs and additional technologies to be discussed subsequently. Maxima and minima in this plot correspond to the 90th and 10th percentile for effluent fractions, respectively, whereas the boxes span the 25th to the 75th percentile. The horizontal line within the box indicates the median value (or 50th percentile). From this analysis, half of all available data for PPCPs treated by MBR correspond to treatment efficiencies between 41–98% (indicated by the box in Fig. 4). The range is broader for CAS, with half of all reports for PPCPs falling between removal efficiencies of 23% and 91%. Available data therefore support a modest improvement in the extent of PPCP removal for MBRs relative to CAS.

When comparing PPCP removal by MBR and CAS on a compound-specific basis, it becomes evident that many of the same species known to be susceptible to CAS (see Table 1) are removed to an equal or greater extent by MBRs. However, PPCP removal can be highly variable between different MBR systems. One example is carbamazepine, for which most MBRs have little to no impact on removal,[30,65,66,70] although at least one report indicates far better performance that yielded effluent levels below detection limits[71] (see MBR data in Fig. 5). These differences may stem from variations in the operating parameters of the MBRs. Similar to CAS systems, there is little agreement regarding the effects of SRT and HRT on PPCP removal. Kimura *et al.*[38] reported that an MBR with a SRT of 65 days displayed greater removal of six acidic PPCPs compared to another MBR with a SRT of 15 days. In contrast, Joss *et al.*[20] found that neither SRT nor HRT affected the removal of seven pharmaceuticals in MBRs. A more nuanced result obtained by other researchers suggests that the dependence of PPCP removal on SRT differs

Table 2 Compounds most recalcitrant to removal *via* traditional wastewater treatment (*i.e.*, solids removal and conventional activated sludge) based upon data available in studies cited herein. For these compounds, less than 30% removal during treatment was reported in at least two thirds of all studies. Analysis was limited to compounds with at least five reports of corresponding influent and effluent concentrations.

Compound (CAS #)	Chemical Structure	Compound Class	Number of Studies (n)	<30% Removal (% of Studies)
Carbamazepine (298-46-4)		Anticonvulsant	48	38 (79%)
Diclofenac (15307-86-5)		Analgesic/Anti-inflammatory	35	23 (66%)
Metoprolol (37350-58-6)		Beta blocker	9	7 (78%)
Iopromide (73334-07-3)		Iodinated Contrast Media	6	5 (83%)
Sotalol (3930-20-9)		Beta blocker	6	6 (100%)

between compounds. Göbel *et al.*[60] found that the removal of sulfonamides in a MBR was independent of SRT, whereas the removal of trimethoprim and several macrolide antibiotics increased with increasing SRT. They suggest that these differences in degradation behavior arise from different substrate dependencies. Sulfonamide degradation appeared to correlate with the ratio of substrate to sulfonamide concentrations in the influent. Trimethoprim and macrolide removal, however, depended on the ratio of substrate to sludge concentration. As the latter ratio decreases with increasing SRT, the resulting increase in the biodiversity of the active biomass leads to more effective transformation of these substances. For a more in-depth discussion of the influence of HRT and SRT on PPCP removal, the reader is referred to the work by Joss *et al.*[20]

B.2. Sand filtration. The treatment of secondary effluent with granular media depth filters, which typically use sand as the filtration medium, is intended to remove suspended solids and turbidity that persist after clarification. For these constituents, removal mechanisms are primarily physical in nature (*e.g.*, straining). PPCP decay also can occur in these systems through further biological degradation within biofilms on the filter media.[60] Incidental removal of PPCPs associated with the retained solids is possible, although this contribution is believed to be small.

A handful of studies report both WWTP influent concentrations of PPCPs and corresponding PPCP concentrations present in the tertiary effluent of sand filters.[34,40,52,71,72] Similar to observations with MBRs, available data indicate a slight increase in the extent of PPCP removal when sand filtration is used for post-secondary treatment (Fig. 6). Roughly 31% of all data from sand filters correspond to PPCP removals greater than 1-$\log_{10}$ concentration unit (32 out of 104 data points), only slightly greater than the value of 25% observed for conventional treatment. From percentile analysis (see Fig. 4), half of all substances exhibit removal efficiencies greater than 69% when sand filtration is employed, compared to a median removal of 61% for CAS.

Because PPCP removal by sand filters is largely, if not entirely, attributable to biological activity, it is difficult to predict from structural and/or physical properties those PPCPs most susceptible to treatment. Furthermore, there remains little consensus as to the influence of operational variables such as hydraulic residence time, hydraulic loading rate, as well as bulk water quality characteristics, on PPCP removal during filtration. Göbel *et al.*[60] observed considerable differences in the extent of trimethoprim removal (15% *versus* 74%) in two sand filters despite comparable hydraulic retention times and hydraulic loading rates per biofilm surface area in each case. They attributed this behavior to differences in the BOD loads to each unit (*i.e.*, higher removal occurred with lower background BOD levels). Evidence also suggests that trends in the relative treatability of PPCPs during sand filtration can likely be inferred from the larger body of empirical results available for biological treatment. Nakada *et al.*[40] considered the removal of 24 different PPCPs during sand

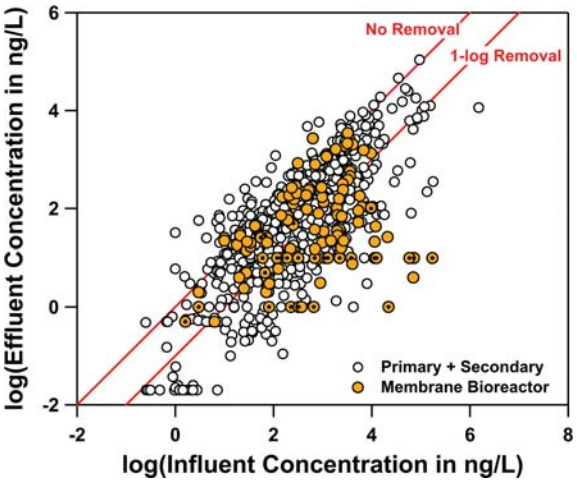


Fig. 3 Comparison plot of PPCP effluent concentration as a function of influent concentration for WWTPs utilizing a membrane bioreactor (MBR) for biological treatment. Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal). For comparison, influent-effluent data obtained with traditional wastewater treatment (data from Fig. 1) are also shown as open circles. Data with center dots indicate instances where effluent PPCP concentrations were below the MDL, in which case effluent data represent the reported MDL.

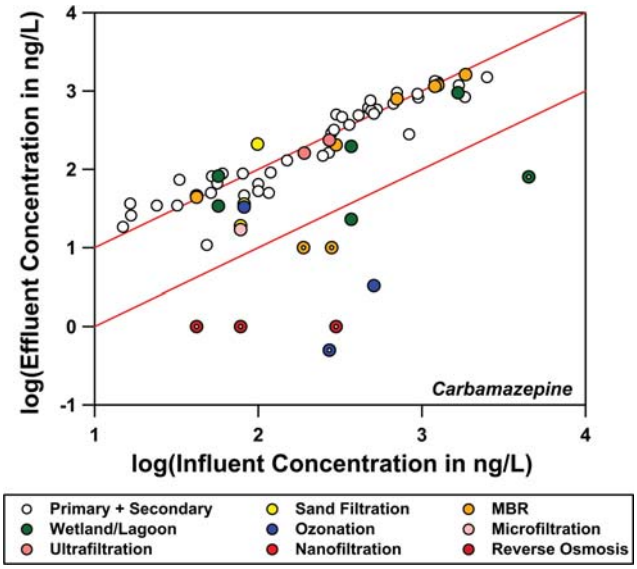


Fig. 5 Influent and effluent concentration comparison for carbamazepine during wastewater treatment with various technologies. Data with a center point indicate those instances where reported effluent concentrations were below the MDL, in which case effluent data represent the reported MDL. Also shown in red are lines indicating no carbamazepine removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal).

filtration. Although they rationalized their observations with sorption tendencies (*i.e.*, correlation to K_{ow} values), the highest removal efficiencies were obtained for compounds we previously identified (see Table 1) as highly susceptible to degradation during CAS (*e.g.*, ibuprofen, estrone, thymol and bisphenol A). Similarly, Göbel *et al.*[60] noted that the subset of PPCPs eliminated to the greatest extent during sand filtration agreed well with those compounds demonstrating increased elimination within MBRs.

B.3. Activated carbon. Activated carbon (AC) in either powdered (PAC) or granular (GAC) form represents the most widely used sorbent in water treatment, traditionally used for the removal of taste and odor causing organic compounds in

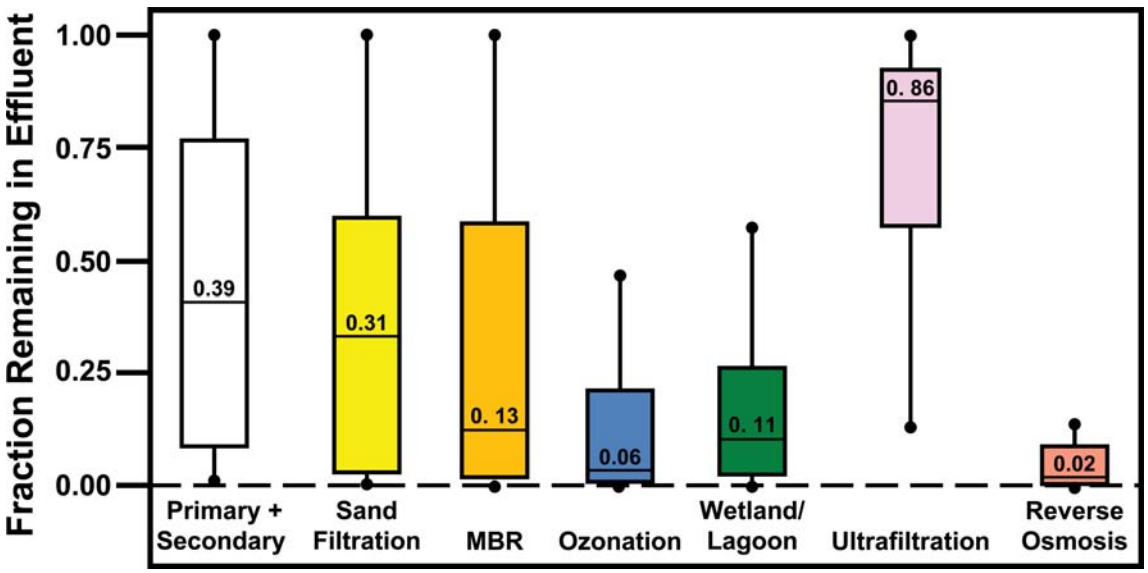


Fig. 4 Box plot comparing PPCP removal efficiencies of the different wastewater treatment technologies considered herein. Plots show the distribution of removal efficiencies, expressed in terms of fraction of PPCP remaining in the treated effluent, for each treatment approach. Maxima and minima correspond to the 90th and 10th percentile for effluent fractions, whereas boxes span from the 25th to the 75th percentile. The solid line in each box represents the 50th percentile (median). Results of percentile analysis are only shown for treatment approaches for which there were over $n = 30$ instances of corresponding plant influent-process effluent data for different PPCPs.

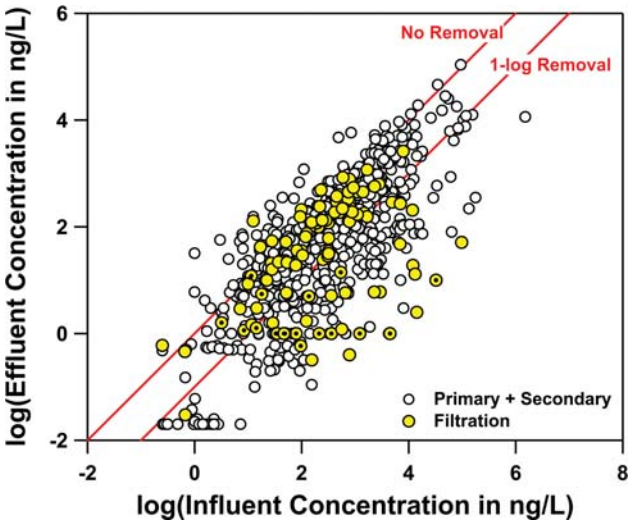


Fig. 6 Comparison plot of PPCP effluent concentration as a function of influent concentration for WWTPs utilizing sand filtration for tertiary treatment of secondary effluent. Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal). For comparison, influent-effluent data obtained with traditional wastewater treatment (data from Fig. 1) are also shown as open circles. Data with center dots indicate instances where effluent PPCP concentrations were below the MDL, in which case effluent data represent the reported MDL.

drinking water.[73] In this capacity, AC is also a recognized route for the sequestration of organic micropollutants, and growing evidence supports its use for removing PPCPs from drinking water.[74,75]

Removal of PPCPs by AC occurs *via* the uptake of a compound onto the surface (*i.e.*, adsorption) or into the porous bulk matrix (*i.e.*, absorption) of the sorbent. Characteristics of AC believed important for performance include surface area, porosity and pore size distribution, and surface acidity or basicity, which affects slurry pH and surface charge.[75,76] For PPCPs, compound hydrophobicity, typically quantified in terms of octanol-water partitioning coefficients (log K_{ow} values), is often used as a predictor of PPCP removal *via* AC. Other solute characteristics including molecular size (*e.g.*, molar volume), hydrophobic surface area, charge and polarity are also believed to influence sorption to some extent.[75,76]

Based largely upon promising results from drinking water treatment, it is assumed that the use of AC will yield significant benefits in wastewater effluent quality.[71] Unfortunately, there are few, if any, available data regarding PPCP removal at pilot or full-scale wastewater treatment facilities incorporating AC. It is widely accepted, however, that the high levels of effluent organic matter (EfOM) in wastewater can be expected to limit AC performance by competing for sorption sites and blocking access to pores within the sorbent structure.[71,74]

Because data from WWTPs utilizing AC do not yet exist, Fig. 7 presents influent and effluent PPCP concentrations from a full-scale GAC test facility treating drinking water with high levels of total organic carbon (TOC),[71] which provides a reasonable estimate of AC performance during wastewater treatment. PPCP removal with GAC at this facility was generally weak. Only acetaminophen exhibited greater than 1-$\log_{10}$ removal, although hydrocodone, diclofenac and pentoxifylline were removed to levels below the effluent MDL. Notably, the authors reported considerably better PPCP removal at another facility with lower TOC levels and more frequent regeneration and replacement of the GAC. For wastewater treatment, therefore, pretreatment to lower TOC and the rate of AC regeneration or replacement will be key design criteria.[71] In particular, fresh AC outperforms aged material due to the accumulation of TOC and other non-target species on the aged sorbent.[74,77] Such considerations may make PAC a more attractive option for wastewater treatment; fresh PAC can be added continuously to the process stream, is not recycled, and its dose can be varied to account for influent quality.[71]

Biological activated carbon (BAC) represents a potentially useful variation on AC treatment. BAC couples PPCP removal *via* sorption with biodegradation that occurs within a biofilm on the sorbent material. The potential benefits of BAC include biological regeneration of the AC *via* degradation of sorbed organic matter over the reactor lifetime, biodegradation of less biodegradable organics that can be initially sequestered on the AC and then degraded within the biofilm, and enhanced biological activity due to the concentrated organic substrate bound to the AC surface.[78] There are multiple instances of BAC application during wastewater treatment,[72,79,80] and it is viewed by some as a "core process" for wastewater reuse and reclamation.[79,80] Fig. 7 includes PPCP data from a full-scale treatment facility incorporating BAC for tertiary treatment.[72] Although the system displayed good removal for several PPCPs, more work is needed to understand the design and operational parameters influencing PPCP removal by BAC.

B.4. PPCP transformation during ozonation. There is rapidly growing interest in the application of chemical oxidation processes for the treatment of organic micropollutants in water and wastewater. This approach utilizes strong oxidants to chemically transform PPCPs ideally into species lacking biological activity that pose no risk to the quality of effluent-receiving waters. Oxidants typically used for this purpose include ozone (O_3) and hydroxyl radical ($^{\bullet}OH$), which is utilized in advanced oxidation processes (AOPs). Because chlorine should not be viewed as a viable treatment option for PPCPs, no influent-effluent data or analyses of PPCP removal during chlorination are presented.

Ozone is used in water treatment as an alternative disinfectant to free chlorine. Ozone is a selective oxidant with electrophilic character that targets π-bond systems, non-protonated secondary and tertiary amines, and reduced sulfur moieties.[81,82] Ozone will, therefore, preferentially react at functional groups on PPCPs with high electron density. In addition to the direct reactions between PPCPs and ozone, indirect oxidation can also occur during ozonation due to transient oxidants generated from ozone decomposition. In water, ozone decays through a series of radical chain reactions that ultimately yield $^{\bullet}OH$, one of the most powerful oxidants in water.[81] Unlike ozone, $^{\bullet}OH$ is a non-specific oxidant capable of degrading a broader range of PPCPs and other organic micropollutants *via* radical addition, hydrogen abstraction or electron transfer mechanisms.[56] The non-specific nature of $^{\bullet}OH$ poses a challenge for wastewater treatment, however; EfOM and other non-target reductants present at much

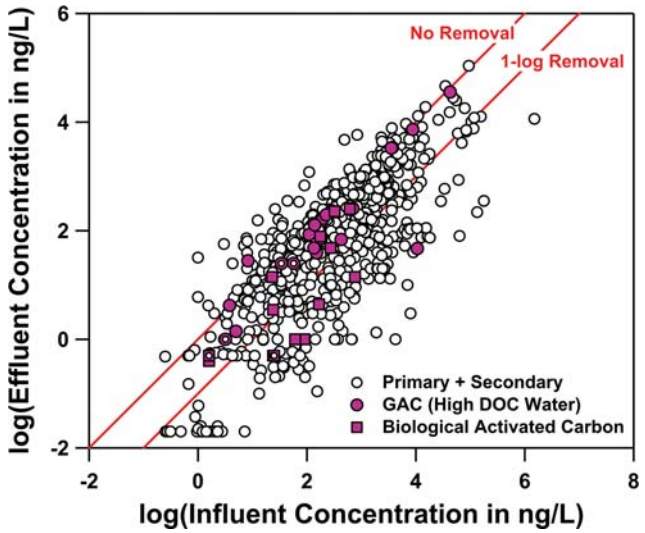


Fig. 7 Comparison plot of PPCP effluent concentration as a function of influent concentration for applications of activated carbon for PPCP removal. As described in the text, data are shown for the application of GAC to a high TOC water source (purple circles) and for the use of biological activated carbon for tertiary wastewater treatment (purple squares). Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal). For comparison, influent-effluent data obtained with traditional wastewater treatment (data from Fig. 1) are also shown as open circles. Data with center dots indicate instances where effluent PPCP concentrations were below the MDL, in which case effluent data represent the reported MDL.

higher concentrations than PPCPs can scavenge most, if not all, $^{\bullet}$OH generated from ozone.

Encouraged by early results demonstrating PPCP transformation by ozone under conditions representative of water treatment,[75,83–85] attention has focused more recently on the treatment efficiency of ozone for PPCPs in wastewater.[40,46,72,86,87] Huber *et al.*[87] conducted a pilot-scale investigation in which ozone was applied to secondary effluents from both a CAS system and a MBR that they spiked with a range of PPCPs. Their results showed nearly complete degradation of macrolides, estrogens, and sulfonamides due to transformation of their tertiary amino groups, phenolic moieties and aniline moieties, respectively. Diclofenac, naproxen and indomethacin were also nearly entirely transformed at doses ($\geq$2 mg O_3/L) that the authors deemed cost-effective for wastewater treatment. Although they found very little variability in ozone performance among the different secondary effluents and total suspended solids (TSS) loadings tested, certain PPCPs were found to be relatively resistant to ozonation. Iodinated X-ray contrast media, which do not react directly with ozone, were only partially oxidized through reaction with $^{\bullet}$OH generated from ozone decay. While the removal of iopamidol, iopromide and iomeprol increased with increasing ozone dose, only 50–60% removal was observed at the highest ozone concentrations investigated (5 mg L^{-1}). Diatriozate, an anionic contrast agent, was most resistant and no statistically significant removal was found at any ozone dose. It is worth noting that the resistance of iopromide to ozonation has also been noted in studies focusing on simulated drinking water treatment,[72,75] suggesting that relative trends in PPCP activity toward ozone established for drinking water can be used to predict their susceptibility during ozonation of wastewater.

Snyder *et al.*[72] conducted bench-scale investigations of PPCP ozonation in surface water and wastewater matrices. For wastewater, their bench-top pilot plant utilized non-disinfected tertiary (filtered) effluent that contained PPCPs at naturally occurring levels. They also presented influent and effluent PPCP concentrations from one full-scale wastewater treatment facility utilizing ozone as a disinfectant. Generally, their results were in relatively good agreement with Huber *et al.*[87] In bench scale studies with tertiary effluent and ozone doses ranging between 2.1 and 8.7 mg L^{-1} (which yielded ozone residuals required for disinfection), removal of most PPCPs was greater than 90%. Moreover, bioassays revealed that the estrogenicity of the treated effluent was reduced relative to that measured before ozonation, consistent with findings of Huber *et al.*[88] and Dodd *et al.*,[89,90] who also found that ozonation diminishes the biochemical activity of many PPCPs. As was also observed in the drinking water studies of Snyder *et al.*,[72] iopromide, musk ketone, dilantin (phenytoin) and meprobamate were most recalcitrant to ozonation, each undergoing only partial (~50% or less) removal. The bench-scale results of Snyder *et al.*[72] also agreed well with their performance monitoring at the full-scale wastewater treatment facility using ozonation. Post-secondary treatment at the facility involved ultrafiltration, pre-oxidation with a small ozone dose, biological activated carbon (BAC) filtration, and then disinfection and chemical oxidation with ozone. The use of this process train resulted in near complete removal for 8 of the 15 micropollutants considered in the plant's secondary effluent; for these 8 species, final concentrations were below the effluent MDL (typically <0.5 ng L^{-1}).

More recent examples of full-scale wastewater ozonation continue to demonstrate promising results for PPCP removal. Fig. 8 compares influent and effluent PPCP concentrations at sites utilizing full-scale wastewater ozonation to concentration data obtained at facilities only employing conventional treatment practices. The data in Fig. 8 are taken from the aforementioned work of Snyder *et al.*,[72] as well as recent investigations by Nakada *et al.*[40] and Hollender *et al.*[46] Nakada *et al.*[40] explored the removal efficiencies of 24 PPCPs *via* post-secondary treatment with sand filtration and ozonation at a municipal sewage treatment facility in Tokyo. Hollender *et al.*[46] considered the fate of 220 micropollutants in a wastewater treatment facility in Regensdorf, Switzerland that employed activated sludge, followed directly by ozonation and then sand filtration. We also note that plant influent data were not reported in Snyder *et al.*,[72] thus ozonated effluent concentrations are compared to values measured in secondary effluent prior to any tertiary treatment processes.

Similar to Snyder *et al.*,[72] full-scale ozonation demonstrations by Nakada *et al.*[40] and Hollender *et al.*[46] report considerably enhanced PPCP removal and far lower PPCP effluent concentrations than those attainable with primary and secondary treatment alone. This improved performance is shown in Fig. 8, with 58% of all data (50 out of 86) corresponding to PPCP removals of greater than 1-$\log_{10}$ concentration unit. Percentile analysis (Fig. 4) reveals that half of all effluent data points achieved removals greater than 94%, while 90% of all data

correspond to removal efficiencies of 54% or higher. Most importantly, several compounds traditionally resistant or only partially transformed during biological treatment are amenable to treatment *via* ozonation. These include carbamazepine (see relevant data in Fig. 5), as well as several compounds within the classes of beta blockers and anti-inflammatory drugs (Fig. 9). These results constitute a clear improvement in PPCP removal over facilities employing only conventional treatment, and ozonation should be viewed as a valuable treatment tool in the event toxicological evidence ultimately leads to regulations that mandate such low PPCP effluent levels.

For wastewater treatment, ongoing and future efforts must aim to better understand the influence of common aquatic chemical variables on ozone performance, as well as the relative importance of O_3 and $^{\bullet}OH$ as active oxidants during ozonation. Immediately after addition, ozone rapidly decomposes due to reaction with wastewater constituents such as EfOM or oxidizable species including nitrite and reduced forms of sulfur. This initial decay, referred to as the instantaneous ozone demand (IOD), can critically influence the efficiency of PPCP removal. Early work by Buffle *et al.*[91] suggested that this initial ozone decay coincided with an increase in $^{\bullet}OH$ to levels typically found in AOPs, which would be beneficial for treatment because of the potency and non-specificity of $^{\bullet}OH$. Conflicting results were reported by Wert *et al.*,[92] however, who found relatively limited $^{\bullet}OH$ available for contaminant destruction during the initial stages of ozone decomposition. Thus, it appears that the relative ozone and $^{\bullet}OH$ exposures may be highly dependent upon the wastewater matrix. One approach to overcome IOD is to use higher ozone doses; based upon kinetic modeling, Nothe *et al.*[93] suggest that 5–10 mg L^{-1} of ozone can degrade even the most resistant micropollutants regardless of EfOM levels. Such doses would, however, increase the cost of treatment while also raising concerns over byproducts generated at such high concentrations.

B.5. PPCP transformation during UV disinfection. During disinfection with high energy UV light, PPCP degradation can occur *via* direct photolysis. For such a scenario, the PPCP must be a chromophore (*i.e.*, capable of absorbing light energy) and the energy of light must be sufficient to break chemical bonds in the PPCP structure. To date, there are no data available on the transformation of PPCPs in wastewater as a result of UV radiation. Although some work has been conducted in systems representative of water treatment, less PPCP removal would be expected in a more complex wastewater matrix, which will include higher levels of organic matter and other light-scattering and absorbing constituents.

In one of the most detailed water treatment studies to date, Canonica *et al.*[94] considered the UV-induced phototransformation of 17α-ethinyl estradiol, diclofenac, sulfamethoxazole and iopromide. In dilute solutions of buffered water at pH 7.0, only modest removals (0.4–27%) were observed at

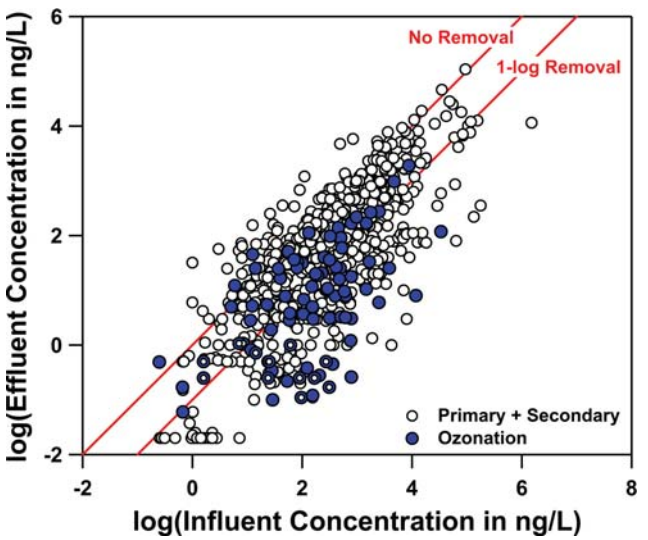


Fig. 8 Comparison plot of PPCP effluent concentration as a function of influent concentration for WWTPs utilizing chemical oxidation with ozone as tertiary treatment of secondary effluent. Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-log concentration unit (90% removal). For comparison, influent-effluent data obtained with traditional wastewater treatment (data from Fig. 1) are also shown as open circles. Data with center dots indicate instances where effluent PPCP concentrations were below the MDL, in which case effluent data represent the reported MDL.

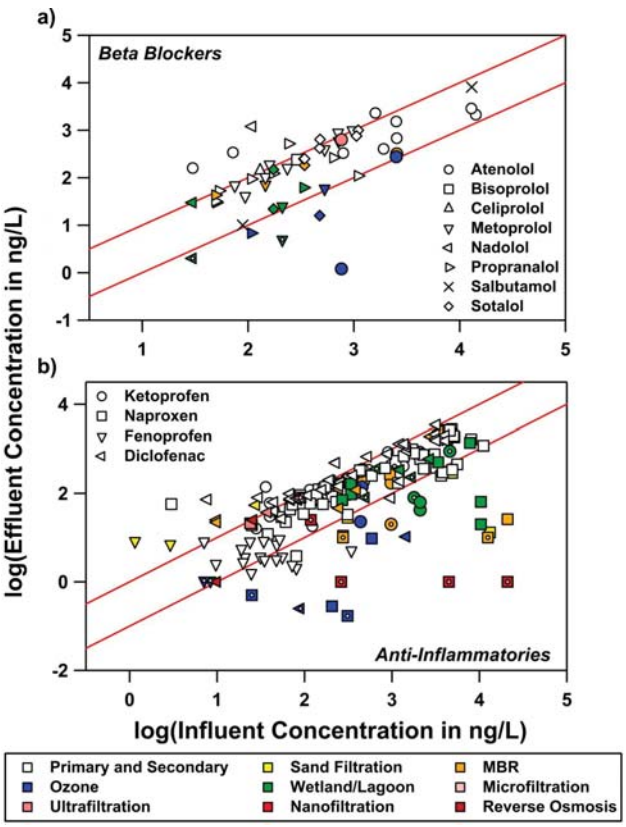


Fig. 9 Influent and effluent concentration comparison of common (a) beta blockers and (b) anti-inflammatory compounds during wastewater treatment with various technologies. Data shape corresponds to different PPCPs, whereas the color of the data represents the different treatment technologies utilized. Data with a center point indicate those instances where reported effluent concentrations were below the MDL, in which case effluent data represent the reported MDL. Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal).

a fluence of 400 J m^{-2}, a standard value for drinking water disinfection using UV. Rosenfeldt *et al.*[95] also conducted work examining the transformation of endocrine disrupting compounds (bisphenol A, 17α-ethinyl estradiol, and 17β-estradiol) upon exposure to UV radiation from either a monochromatic low pressure UV lamp or a polychromatic medium pressure UV lamp. As in the study by Canonica *et al.*,[94] experiments were conducted in model laboratory systems or with samples of natural surface waters, and limited removal (<20%) was observed due to direct phototransformation.

B.6. PPCP transformation during advanced oxidation processes. Advanced oxidation processes (AOPs) encompass treatment technologies that rely on the production of $^{\bullet}OH$ or other radicals, which act as strong oxidants capable of degrading recalcitrant compounds. Many different AOP technologies for radical production exist, including heterogeneous photocatalysis using TiO_2 in combination with UV light or solar irradiation, Fenton's and photo-Fenton's reagent, ozone in combination with peroxide (H_2O_2) or UV light, UV light in combination with H_2O_2, electrolysis, sonolysis, ionizing radiation, ferrate reagent and others. The majority of research relating to PPCP degradation by AOPs has focused on heterogeneous photocatalysis, ozone-based AOPs and (photo-)Fenton's reagent.[96] However, studies investigating other technologies are currently emerging. Most studies to date have focused on PPCP removal from laboratory solutions or surface waters, while investigations using wastewater remain scarce. Of 80 recently reviewed papers addressing the removal of PPCPs by AOPs,[96] only seven used WWTP effluents as the matrix. Of those studies, four were conducted in pilot- or full-scale systems, whereas the others were performed at a laboratory scale. As a result of this scarcity of wastewater data, we did not include AOPs in our influent-effluent analyses comparing unit operation performance.

While often viewed as a promising treatment approach, the advantages of AOPs over conventional chemical oxidation methods (*e.g.*, ozonation) remain unclear. In a study involving a wastewater matrix and 36 PPCPs and other micropollutants, Snyder *et al.*[72] determined that advanced wastewater treatment by O_3/H_2O_2 only marginally improved PPCP removal relative to treatment with O_3 alone. Similarly, Ternes *et al.*[86] showed that AOPs applied to wastewater (O_3/H_2O_2 and UV/H_2O_2) did not enhance the removal of iodinated X-ray contrast media, which are quite recalcitrant to O_3. These findings are in contrast to those obtained for AOP application to distilled or surface waters matrices,[95,97] most likely due to the role of EfOM as a radical scavenger.

Notably, different AOP technologies can yield different degradation pathways for the same compounds. In a pilot-scale study of the removal of diclofenac by photo-Fenton's reagent using a compound parabolic collector (CPC) exposed to sunlight, complete oxidation was attained within 60 min, and complete mineralization in 100 min.[98] Comparison with other oxidative treatments, namely O_3, UV/H_2O_2 and photolysis, showed that degradation pathways differed between these AOPs. Similarly, Radjenovic *et al.*[99] found similar, but not identical pathways for the degradation of atenolol by heterogeneous photocalatyis and homogeneous photo-Fenton treatment in the same CPC setup. Furthermore, the photo-Fenton process was found to be more effective for PPCP removal compared to heterogeneous photocatalysis.[99,100] Thus, not only PPCP removal efficiencies but also PPCP transformation pathways will need to be evaluated for AOPs when considering their application to wastewater. While AOPs can reduce the estrogenicity[2] and antimicrobial activity[90] of PPCPs, metabolites may exhibit other toxicity mechanisms. For example, the toxicity of wastewater effluent, measured by three bioassays (*Daphnia magna*, *Pseudokirchneriella subcapitata* and *Lepidium sativum*), was not fully eliminated upon treatment by heterogeneous photocatalysis using TiO_2.[101]

B.7. PPCP removal using membrane filtration. Membrane filtration for the removal of pathogens, micropollutants and salts has gained importance in drinking water production over the past decade. More recently, this technology has also attracted interest as a method to improve PPCP removal from wastewater, particularly in instances of wastewater reclamation and reuse. Membrane application to full-scale or even pilot-scale wastewater treatment systems is still somewhat rare, but there is an increasing body of literature reporting on this topic.

In contrast to MBRs, where the function of membranes is predominantly the retention of sludge for biodegradation, membrane filtration technologies function by rejecting constituents due to pore size restrictions or electrostatic repulsion. Adsorption onto the membrane also can contribute to compound rejection, especially for neutral and hydrophobic substances.[102] Membranes are categorized as reverse osmosis (RO), nanofiltration (NF), ultrafiltration (UF) or microfiltration (MF) membranes, depending on their molecular weight cut-off (MWCO). Different membrane types are typically installed in series, with low-pressure membranes (MF or UF, alone or as a MBR) providing pre-treatment, followed by one or more units of tighter, high-pressure membranes (RO or NF) for micropollutant removal. Based on the typical size of PPCPs, only RO and NF membranes are suited for PPCP removal by purely a size exclusion mechanism. However, if electrostatic repulsion or adsorption contributes or is the dominant mechanism, membranes with pores larger than the compound of interest have been found to lead to PPCP retention.[103] Kimura *et al.*[104] reported that negatively charged disinfection byproducts, PPCPs and endocrine disrupting compounds in Milli-Q water were rejected by RO/NF membranes independent of their molecular size. Conversely, RO membranes have also been found to retain compounds to a lesser degree than expected based on their molecular size. This was the case for the hormones estrone and estradiol,[105] as well as for two trihalomethanes[106] in actual and simulated wastewater. This membrane breaching was attributed to cross-membrane diffusion of the compounds over longer operation times.

The efficiency of PPCP removal by membrane filtration depends on a multitude of parameters. Besides MWCO, membrane material properties such as hydrophobicity, surface roughness, and charge will affect PPCP removal.[107] In addition, depending on the retention mechanism, different physical-chemical parameters of the individual substances can influence their retention. Critical parameters include the molecular weight and size, acid dissociation constant (pK_a), octanol-water partitioning coefficient (K_{ow}), polarity and aqueous diffusion coefficient.[103,107] For example, the retention of antibiotics from the

wastewater of a veterinary antibiotic production plant by RO/NF was a function of the molecular weight of the individual compounds.[108] Similarly, the retention of 11 neutral endocrine disruptors and PPCPs in distilled water by a polyamide RO membrane was correlated to the molecular weight of the individual compounds.[109] The retention mechanism in both cases was therefore attributed to size exclusion. In contrast, the retention of the same 11 compounds by cellulose acetate membranes increased with increasing polarity of the compound, indicating that mechanisms other than size exclusion influenced retention.[109]

The composition of the feed water, in particular the organic matter content, water hardness and pH, also influence retention efficiency.[107] As with chemical oxidation strategies and activated carbon, the high EfOM content in wastewater represents an important distinction between membrane treatment for drinking water and wastewater. The effect of EfOM on PPCP rejection precludes simple extrapolation from drinking water to wastewater applications. The effect of membrane fouling by EfOM on wastewater treatment efficiency therefore warrants further investigation. Generally, EfOM has been found to exert a retention-enhancing effect on the removal of charged compounds by various NF and RO membranes.[105,106,110,111] This effect was attributed either to modification of the membrane surface charge,[106,110,111] to interactions of the EfOM with the compounds,[105,111] or to restriction of the pore size in the case of loose membranes.[110] If adsorption to the membrane is the main rejection mechanism, however, the presence of EfOM can also be detrimental. For example, Comerton *et al.*[112] reported that the rejection of the hydrophobic compound gemfibrozil decreased in the presence of EfOM, which was attributed to competition for adsorption sites.

Finally, operational conditions such as the transmembrane pressure[105] and the permeate flux rate[102] can affect PPCP retention. The importance of taking into account actual operational conditions including flux, recovery and membrane fouling in laboratory-scale experiments was stressed by Drewes *et al.*,[106] who found that laboratory experiments underestimate contaminant removal compared to full-scale systems.

In a recent extensive series of full- and pilot-scale investigations of wastewater treatment by different membrane types, makes and configurations, Snyder *et al.*[71] concluded that UF and MF were only effective for steroid removal, unless used in an MBR configuration, and that generally, MF outperformed UF. UF was also found to have limited impact on PPCP removal in an earlier work by this group.[72] Data from these studies pertaining to influent PPCP levels and their corresponding MF and UF effluent concentrations are summarized in Figs. 10a and 10b, respectively. We note that influent data for UF studies correspond to PPCP levels reported in secondary effluent because levels in the raw influent were not available. These figures clearly illustrate the slight improvement in effluent quality afforded by MF and UF relative to conventional treatment practices for wastewater. Removal of 1-$\log_{10}$ concentration unit is observed for 64% (16 out of 25) of available plant influent- MF effluent concentration data, whereas only 9% of UF data (4 out of 44) correspond to removal greater than 1-$\log_{10}$ concentration unit.

In contrast, Snyder and colleagues[70,71] report that wastewater treatment trains utilizing NF and RO, preceded by appropriate techniques to improve secondary effluent quality to a level suitable for membrane separations, achieve the best removal efficiencies for PPCPs. NF and RO effluent data from Snyder *et al.*[71] and Kim *et al.*[70] are summarized in Fig. 10c and 10d, respectively, illustrating the exceptional PPCP removal efficiencies exhibited by NF and RO membranes for the vast majority of compounds. Roughly 90% of all RO effluent data correspond to PPCP levels below the method detection limit for analysis, which was typically on the order of 1–5 ng L^{-1} (data points indicated in Fig. 10d by a center dot). Comparable results were reported for NF; all PPCP concentrations in NF effluent correspond to removal greater than 1-$\log_{10}$ concentration unit (16 out of 16) and all but one compound (TCEP) were removed to levels below analytical MDLs.

PPCP removal in RO and NF systems is far superior to that achieved in treatment trains utilizing other tertiary treatment operations considered herein. While we had insufficient data for NF and MF to conduct a comparison of percentiles, analysis of the available UF data showed that this membrane provides little, if any benefit, over secondary treatment (see Fig. 4). RO, in contrast, is characterized by very high PPCP removal efficiencies. Half of all data correspond to removals greater than 98%, whereas only about 10% of all RO effluent concentration data exhibited removal less than 85% (see Fig. 4). Notably, the list of PPCPs rejected by RO includes carbamazepine (see data in Fig. 5), which is notoriously difficult to remove by biological treatment. RO is also among the most effective treatment approaches for iodinated contrast media (Fig. 11), which as a class are recalcitrant to biological treatment and only partially degraded *via* chemical oxidation methods. A small subset of compounds, however, have been occasionally detected in RO permeate, and their breakthrough cannot be rationalized by their physical-chemical properties. In Snyder *et al.*,[71] membrane breaching frequently was reported for DEET, meprobamate, gemfibrozil and sulfamethoxazole, all of which were relatively poorly removed during the treatment steps preceding RO (MBR, UF or MF), and were thus present at elevated concentrations in the RO feed. If a RO double-pass was installed, however, these remaining micropollutant traces could be fully removed during the second pass.[71]

Several aspects of membrane treatment of wastewater have not conclusively been addressed to date. In a recent overview of the advantages and drawbacks of NF, van der Bruggen *et al.*[113] identified several parameters that warrant further investigation. These include membrane fouling, treatment of concentrates, and the need for modeling and simulation tools. First steps toward resolving this last aspect, the development of simulation tools, have been attempted by Kim *et al.*,[70] who constructed a transport/rejection model for neutral and charged compounds based on membrane properties, which differentiated between convective and diffusive contaminant transport through the membranes. As the authors point out, however, their model lacks predictive capabilities, and thus needs further refinement.

B.8. Passive effluent treatment technologies: Soil aquifer treatment, wetlands, and treatment lagoons. There is growing interesting in passive tertiary treatment techniques that utilize attenuation processes in natural systems as a final polishing step for wastewater effluent. These include soil aquifer treatment,

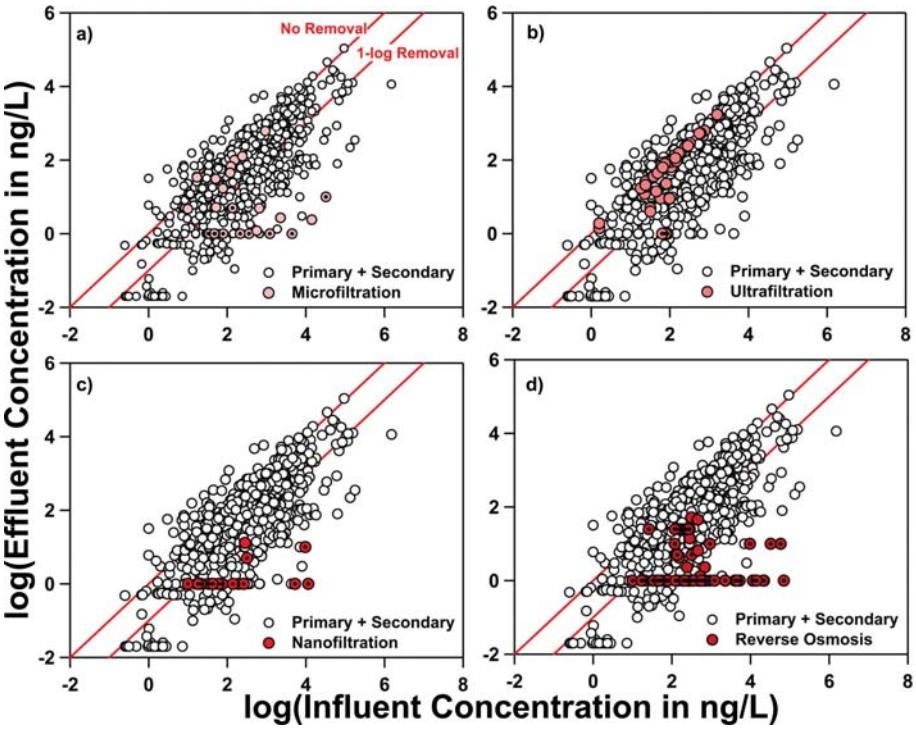


Fig. 10 Comparison plot of PPCP effluent concentration as a function of influent concentration for WWTPs utilizing (a) microfiltration, (b) ultrafiltration, (c) nanofiltration and (d) reverse osmosis for tertiary treatment. Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal). For comparison, influent-effluent data obtained with traditional wastewater treatment (data from Fig. 1) are also shown as open circles. Data with center dots indicate instances where effluent PPCP concentrations were below the MDL, in which case effluent data represent the reported MDL.

natural and constructed wetlands, and treatment lagoons. Unlike most oxidative or separative tertiary treatment options, these approaches hold the advantage of operating at low energy and cost, and do not require sludge or brine removal.

During aquifer recharge with treated wastewater effluent, soil aquifer treatment (SAT) represents a sustainable strategy that can mitigate potential risks associated with persistent chemicals including PPCPs.[114] SAT takes advantage of natural subsurface processes that occur primarily in the vadose (unsaturated) zone to treat reclaimed water that is subsequently stored in the aquifer and eventually extracted for municipal use[115] (*i.e.*, managed underground storage and recovery operations).[116] Most often, recharge projects utilize rapid infiltration ponds (or surface spreading basins) built on permeable sediments to introduce treated effluent into aquifers, a process characterized by fluctuating organic matter concentrations and variable redox potentials arising from the repeated wetting and drying cycles associated with multiple recharge events.[117]

The fate of effluent-derived PPCPs during SAT has been studied either using bench-scale column studies constructed from aquifer materials or *via* field-scale monitoring of PPCPs at sites utilizing treated effluent for recharge.[115,118–124] These studies have generally revealed that a wide variety of PPCPs can be further degraded during SAT including anti-inflammatories, analgesics, steroids and some endocrine disruptors,[118,119,122,123] with biodegradation representing the most important attenuation process.[118,122,124] Certain compounds, particularly those that are most resistant to biological degradation, are recalcitrant, however; effluent-derived carbamazepine and primidone were reported to persist in the subsurface at some reuse facilities for as long as 6 to 8 years.[118,119]

PPCP removal in wetlands and lagoons can occur by multiple mechanisms, including adsorption onto the wetland matrix, aerobic and anaerobic biodegradation, and photodegradation in the case of surface flow wetlands and lagoons. Wetlands and lagoons typically have longer HRTs than conventional treatment systems. This restricts their use to situations where a large footprint can be accommodated or where the wastewater volume is small.

While nutrient removal in wetlands has been extensively investigated, information regarding the degradation of PPCPs has only recently started to emerge. In an early study, Gross *et al.*[125] investigated the fate of selected PPCPs and other wastewater-derived contaminants during river transport and subsequent passage through a constructed wetland with a residence time of 2–4 days. They reported significant removals of gemfibrozil, ibuprofen and its metabolite hydroxyibuprofen in the wetland, although this effect was small compared to attenuation during river transport.

Matamoros and co-workers[126–131] have extensively investigated the fate of PPCPs in constructed wetlands of different configurations. In a performance comparison of two planted subsurface horizontal flow wetlands with different water depths, they found that PPCP removal was better in the shallow wetland. This finding was attributed to the less anaerobic environment of the shallow wetland, which therefore had a less negative redox

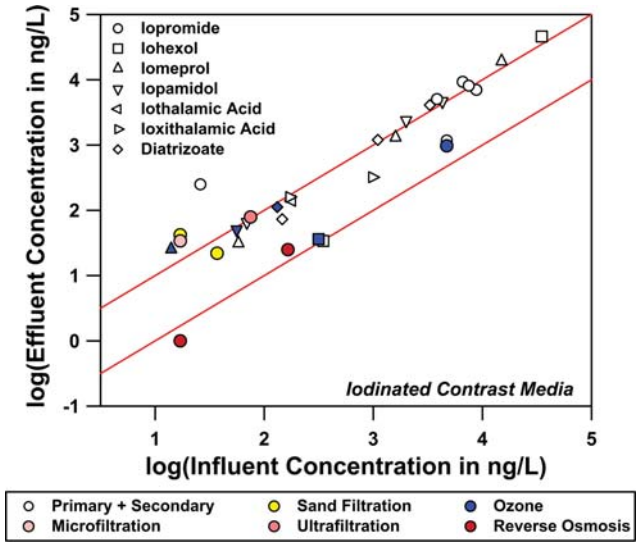


Fig. 11 Influent and effluent concentration comparison of common iodinated contrast media during wastewater treatment with various technologies. Data shape corresponds to different PPCPs, whereas the color of the data represents the different treatment technologies utilized. Data with a center point indicate those instances where reported effluent concentrations were below the MDL, in which case effluent data represent the reported MDL. Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal).

potential.[129,130] Of the PPCPs tested in these two studies, salicylic acid and carboxy-ibuprofene were removed at >80%, ibuprofen, hydroxyl-ibuprofen and naproxen at 50–80%, carbamazepine at <50%, whereas clofibric acid, ketoprofen and diclofenac were recalcitrant. Degradable PPCPs were removed by biodegradation, whereas musks were removed by adsorption onto the gravel bed. In a subsequent study, Matamoros *et al.*[127] compared PPCP removal in pilot-scale vertical subsurface flow wetlands (VFCW) to sand filters. They found that both systems operated well at the design loading rate, but the VFCWs maintained higher removal rates during overload conditions. Furthermore, the vegetation present in the VFCWs helped to prevent clogging. Finally, operation under unsaturated flow conditions achieved better removals than saturated flow conditions. Most recently, these authors compared the removal of 13 substances from wastewater treated by small-scale systems consisting of a sedimentation step followed by different biological treatment methods. The biological treatment steps included five horizontal-flow wetlands, four vertical-flow wetlands, sand filters and biofilters.[128] It was found that removal in all systems was >80%, except for the more recalcitrant compounds carbamazepine, diclofenac and ketoprofen. However, the vegetated, vertical-flow wetlands consistently performed better than the other systems. This was attributed to the unsaturated flow and presence of vegetation, which results in better oxygenation compared to the horizontal wetlands. As a summary of their work, the authors advocate planted VFCWs as an appropriate treatment option because they require lower HRTs and achieve better removal than horizontal flow configurations.

Similar to wetlands, PPCP removal in treatment lagoons or ponds has not received much attention to date. From one of the few studies published on this topic, it appears that lagoons perform as well as CAS treatment systems for the degradation of biodegradable compounds.[32] For more recalcitrant compounds, however, lagoons have been found to outperform CAS systems. This was the case for gemfibrozil and diclofenac removal in three Canadian lagoons treating municipal wastewater,[32] as well as for carbamazepine removal in French treatment plants consisting of trickling filters followed by ponds, or of a sequence of ponds alone.[61] In the latter case, the enhanced removal of carbamazepine compared to CAS systems was attributed to adsorption onto organic matter as well as photodegradation in the maturation ponds.

The efficiency of PPCP removal in a combined lagoon/wetland treatment system was investigated by Conkle *et al.*,[132] who studied the fate of PPCPs in wastewater that first entered a series of aeration lagoons, followed by a constructed wetland, UV disinfection, and finally a natural wetland. Of the nine PPCPs followed throughout this treatment, most were removed to greater than 1-$\log_{10}$ concentration unit. The two most recalcitrant compounds, carbamazepine and sotalol, were removed to a lesser extent (52 and 81%, respectively). Overall, the authors concluded that this natural treatment setup performed better than conventional wastewater treatments with respect to PPCP removal, which they attributed to the longer residence time of the system (~30 days). Similar conclusions were presented by Hijosa-Valsero *et al.*,[126] who monitored the removal of selected PPCPs from primary treated municipal wastewater in three full-scale hybrid systems consisting of different arrangements of ponds, surface and subsurface wetlands in series. The observed removal efficiencies were compared to those obtained in a conventional WWTP, and removal in the passive systems was generally greater. Interestingly, the recalcitrant compound diclofenac, which was not removed in the WWTP, was degraded by 65–87% in the passive systems. The improved removal efficiency was attributed to the coexistence of different microenvironments in the passive system, which leads to a variety of parallel pathways for PPCP degradation. In WWTPs, in contrast, the physicochemical conditions tend to be more homogenous, limiting the number of degradation pathways that exist.

A compilation of influent and effluent data from studies documenting PPCP removal in lagoon and wetland treatment systems[18,126,128,131–133] confirms that such passive or natural treatment approaches perform favorably relative to conventional wastewater treatment systems (Fig. 12). Using the removal of 1-$\log_{10}$ concentration unit as a basis for performance comparison, 48% of available data (38 out of 79) achieve this threshold at facilities utilizing lagoons and/or wetlands (natural or constructed). Furthermore, percentile analysis indicates that these treatment methods yield PPCP removal on par to ozonation (see Fig. 4). In fact, 90% of effluent concentration data from facilities using lagoons and/or wetlands correspond to removal of at least 43%, which is an improvement over CAS or MBRs for biological treatment. While promising, additional research and full-scale performance data are needed to further validate the early performance reports for these natural or passive treatment methods. Also, the advantages conferred by these approaches (*e.g.*, lower energy requirement and operating costs) must be weighed against the requirement of a considerably larger spatial footprint.

III. Predicting and minimizing PPCP occurrence in wastewater effluents

A. Recommendations for optimizing PPCP removal

In choosing between possible biological treatment options (*e.g.*, CAS, MBR, *etc.*) to optimize PPCP removal, it is generally observed in Figs. 1 and 2 that removal by CAS only exceeds 1-$\log_{10}$ concentration unit (or 90%) for a relatively small subset of PPCPs (Table 1). Interestingly, existing influent and effluent data indicate that for conventional biological treatment, PPCP removal appears relatively invariant with respect to microbial community composition, as well as the HRT and SRT conditions applied. We therefore conclude that the maximum removal potential by conventional biological treatment likely cannot be expanded much beyond current performance through simple manipulation of process operating conditions. Rather, it appears that improvements can only be achieved by upgrading to a more advanced biological treatment technology such as MBRs, although increases in PPCP removal may only be marginal at best (see Fig. 4). Alternatively, tertiary treatment approaches in parallel that couple biodegradation with other attenuation processes appear promising. These include biological activated carbon (BAC), which couples biodegradation and sorption, or natural/constructed wetlands, in which a multitude of PPCP removal mechanisms can occur simultaneously with biodegradation.

Of course, PPCP removal also can be augmented using tertiary treatment approaches that do not rely on biodegradation. The level of PPCP removal afforded by membrane technologies may be most appropriate when high quality effluent is desired (*e.g.*, indirect or direct potable reuse). Ozonation may be more broadly applicable for WWTPs simply aiming to lower effluent PPCP loads because it can be directly applied to secondary effluent[46] without the extensive pretreatment required for NF or RO. Evidence also suggests that other chemical oxidation approaches including AOPs hold limited, if any, real advantage over ozonation.[72]

Notably, there may be additional benefits for the sequential application of ozone and BAC to secondary effluent. During their full-scale evaluation of wastewater ozonation, Hollender *et al.*[46] recommended the use of a biological sand filter post-ozonation to remove byproducts of oxidation including nitrosodimethylamine (NDMA) and biologically assimilable carbon such as aldehydes. Treatment of ozonation effluent with BAC should provide comparable, if not greater, benefit due to the nature of the activated carbon sorbent used as the filter media. We caution, however, that these recommendations are based entirely on lowering PPCP effluent concentrations and do not fully consider the economic impact of increased reliance on advanced treatment technologies, which is discussed in greater detail subsequently.

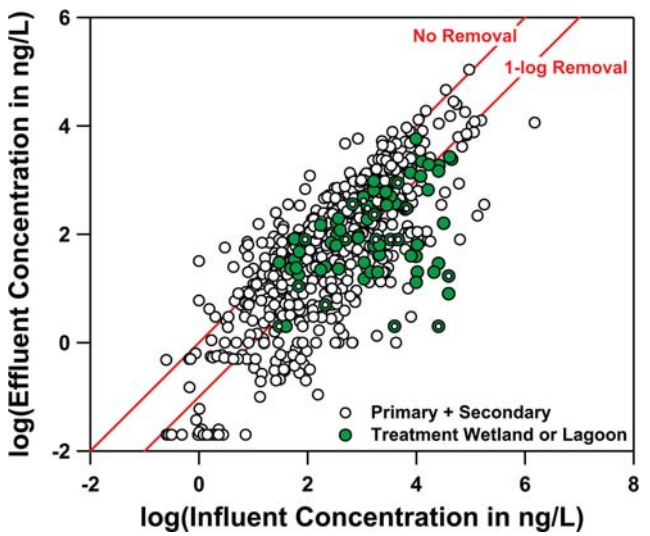


Fig. 12 Comparison plot of PPCP effluent concentration as a function of influent concentration for WWTPs utilizing wetland or lagoon treatment systems. Also shown in red are lines indicating no PPCP removal and removal corresponding to 1-$\log_{10}$ concentration unit (90% removal). For comparison, influent-effluent data obtained with traditional wastewater treatment (data from Fig. 1) are also shown as open circles. Data with center dots indicate instances where effluent PPCP concentrations were below the MDL, in which case effluent data represent the reported MDL.

B. Predicting PPCP removal efficiency and occurrence in treated effluent

Predictive models that estimate PPCP persistence as a function of the compound's physical and chemical properties have been developed with varying degrees of success for specific water treatment technologies.[43,70,75,76,134] Unfortunately, to date no single approach has emerged that accurately predicts PPCP removal during wastewater treatment over a wide range of treatment technologies, water quality conditions, and PPCP compounds and compound classes.

Predictions of PPCP persistence in effluent will likely have to be based on experimentally gathered evidence rather than simple physical and chemical principles governing their fate during treatment. For example, several substances are almost universally shown to persist during conventional wastewater treatment. From our literature survey, PPCPs for which a removal of less than 30% has been consistently reported include carbamazepine ($n_{total} = 48$; 79% of which report <30% removal), diclofenac (35; 66%), metoprolol (9; 78%), sotalol (6, 100%), and iopromide (6; 83%) (Table 2). Our analysis is corroborated by others; carbamazepine and diclofenac have been found in >90% and >80%, respectively, of surveyed river water samples in Europe.[135] Glassmeyer *et al.*[136] detected carbamazepine in >80% of samples in and around 10 WWTPs across the United States. Miege *et al.*,[137] who conducted a similar review of PPCP occurrence in WWTPs, reported the presence of carbamazepine in all of 63 effluents considered, while diclofenac and metoprolol were also found with high regularity (85% and 97% of effluents evaluated, respectively). It can thus be concluded that these compounds are among the PPCPs most resistant to biodegradation. Moreover, any of these species could serve as a good indicator of wastewater inputs to surface water; they are consistently present in influent at concentrations well above MDLs, are recalcitrant to removal during conventional treatment, and municipal wastewater effluent constitutes an important entry route into surface water.

Several methods have also been proposed utilizing the occurrence of select PPCPs with well-characterized behavior in WWTPs, referred to as indicator or marker compounds, to evaluate treatment system performance. As indicators of biodegradation-based treatment, two approaches have been proposed. Several authors suggest the use of enantiomeric ratios of substances such as naproxen[128] or propranolol[138] to determine the extent that a wastewater has undergone biological treatment. This method is based on the insight that microorganisms preferentially degrade one enantiomer in a racemic mixture, whereas dilution would affect both enantiomers equally. Other studies[136,139] suggest monitoring the ratio of biodegradable PPCPs to recalcitrant species in wastewater effluent, a ratio that should decrease with increasing treatment efficiency. Based on the data compiled for this review, suitable choices for biodegradable compounds include acetaminophen, ibuprofen, thymol, aspirin or salicylic acid (Table 1). Hormones such as estrone and estradiol could also be used, but their effluent concentrations are frequently below method detection limits. Among the most frequently detected biologically recalcitrant compounds, we propose the use of carbamazepine, diclofenac, metoprolol, or sotalol (Table 2), as well as the class of iodinated X-ray contrast media (Fig. 11).

WWTPs employing tertiary treatment may require a different set of indicators compounds. For example, biologically recalcitrant carbamazepine and diclofenac are readily degraded during ozonation, whereas several X-ray contrast media are not.[46] Using three sets of indicator compounds corresponding to (i) biodegradable PPCPs, (ii) biologically recalcitrant but oxidatively degradable PPCPs (*e.g.*, carbamazepine and diclofenac), and (iii) PPCPs recalcitrant to both biodegradation and chemical oxidation (*e.g.*, iopromide or other iodinated contrast media) could provide information regarding not only the overall treatment system efficiency, but also the treatment stage where failure occurs. For example, Dickenson *et al.*[140] recommended dilantin (phenytoin), DEET, meprobamate, and iopromide as indicators to assess the conditions during ozonation of tertiary treated wastewater for indirect potable reuse processes. These species represent those most resistant to both biodegradation and direct reaction with ozone. Thus, detection of these PPCPs in the absence of others known to be readily degradable by ozone (*e.g.*, carbamazepine and diclofenac) would indicate an ozone system operating as expected. Alternatively, the absence of these indicator species after ozonation would indicate high exposure levels to $^{\bullet}OH$ capable of degrading nearly all PPCPs. Identification of carbamazepine or diclofenac after ozonation would suggest inefficient oxidizing conditions.

We note that an alternative approach utilizing bulk water parameters as indicators for ozonation performance was explored by Wert *et al.*[141] They suggested a simple method for monitoring PPCP removal that relies upon changes in UV_{254} absorbance and color of the wastewater upon ozonation. Oxidation of ozone-reactive compounds was found to correlate well with a reduction in UV_{254} absorbance between 0–50%, and PPCPs that react predominantly with hydroxyl radicals correlated well with a UV_{254} reduction of 15–65%. Similarly, the loss of true color also could be correlated with the extent of PPCP degradation during ozonation.

IV. Current and future challenges posed by PPCPs for wastewater management

Despite recent progress toward better understanding of PPCP removal during water treatment, many challenges associated with PPCPs in wastewater remain. Here, we introduce a selection of issues that will be critical for the development of reliable technologies for PPCP removal and sustainable practices for wastewater management. These include emerging methodologies for PPCP analysis and monitoring; byproducts generated from the transformation for PPCPs during wastewater treatment; and potential challenges associated with an increased reliance on the advanced treatment technologies that have proven thus far to be best suited for PPCP removal. We do not address the pressing need for ecotoxicological data that convincingly demonstrates the adverse impacts associated with exposure to PPCPs or PPCP mixtures at levels anticipated in wastewater effluent, which is beyond the scope of this review. For a detailed treatment of this topic, the reader is referred to a review of pharmaceutical ecotoxicology by Fent *et al.*[142]

A. Analytical approaches for identification of unknowns and real-time PPCP monitoring

Current frontiers in PPCP analysis are geared toward the identification and quantification of yet unidentified species, as well as transformation products generated during treatment. The identification of such unknown substances involves the application of high-resolution mass spectrometry (MS) methods, such as (quadrupole) time-of-flight-MS/MS and linear ion trap MS. These techniques allow the identification of non-target compounds in the absence of analytical standards. Applications of high-resolution mass spectrometry techniques to identify non-target compounds have recently been demonstrated.[143,144]

Another growing area in PPCP analysis is the development of real-time detection and quantification tools, which allow the continuous monitoring of PPCPs in effluents. Vanderford *et al.*[145] presented a mass spectrometry-based method capable of real-time monitoring of triclosan and its degradation products during chlorination. In this approach, samples were directly injected into a mass spectrometer, thereby avoiding the need for chromatographic separation, sample quenching or derivatization. While this technique has to date only been applied to controlled lab experiments, its expansion to applications involving real effluents could be envisioned.

For real-time monitoring, sensor-enabled technologies may prove more suitable than MS-based techniques. Sensors rely on species detection *via* a recognition element, such as antibodies, enzymes or membrane-imprinted polymers. An overview of the current (bio)sensor-based applications for the detection of organic contaminants in environmental samples is presented by Rodriguez-Mozaz *et al.*[146,147] Compared to mass spectrometry applications, sensor-based technologies hold many favorable attributes. Potentially they can consume less sample volume, do not require trained personnel for operation, are less sensitive to matrix effects and are more cost-effective. Multi-analyte detection, however, remains challenging,[147] and more studies evaluating the sensitivity, selectivity and robustness of (bio)sensor-based technologies in complex environmental matrices are required.

B. Next generation treatment byproducts

PPCPs undergo, to varying extents, chemical and/or biologically mediated transformations during wastewater treatment. As previously mentioned, however, degradation should not be equated with removal. All chemical and biological reactions result in the formation of products, many of which may share structural similarities with or retain the biochemical activity of the parent PPCPs from which they are derived.

To date, most concern has focused on the potential formation of hazardous transformation products during chlorination of PPCPs. Laboratory investigations with model systems have convincingly demonstrated that chlorination of common PPCPs can lead to the formation of known toxicants and probable carcinogens. Rule *et al.*[148] demonstrated that free chlorine doses typically used in water treatment could react with the common antimicrobial triclosan to produce chloroform. Likewise, Bedner and MacCrehan[149] found that chlorination of acetaminophen under conditions simulating wastewater disinfection led to the production of several products, including the known toxicants 1,4-benzoquinone and N-acetyl-p-benzoquinone imine, which are associated with lethal acetaminophen overdoses.

Of additional concern are transformation products uniquely formed during PPCP chlorination.[150,151] At low doses or short contact times, reaction with chlorine is likely to only produce small modifications in the parent compound structure. Dodd and Huang[152] found that trimethoprim reacts readily with free chlorine yielding products that were predominantly multi-chlorinated and hydroxylated. Early work examining the chlorination of 17β-estradiol[153,154] observed similar phenomena; seven transformation products were identified including 2,4-dichloro-17β-estradiol, monochloroestrone, and 2,4-dichloroestrone.

These unique species generated during chlorination represent the next generation of disinfection byproducts. They are viewed by many as a cause of concern with respect to their biological activity and possible toxicity, particularly mono- and di-chlorinated products that largely retain the structure of the parent PPCP. To date, several studies have employed *in vitro* cell assays to evaluate changes in biochemical activity induced by chlorination. The most widely applied of these approaches is the YES (Yeast Estrogen System) assay, which screens for estrogenicity. Several studies have used the YES assay or similar to conclude that chlorination of estrogenic hormones and endocrine disrupting compounds yields end products of lesser or no estrogenicity.[155,156] As analytical methods for detecting, identifying and isolating these transformation products become more readily available, future research must continue to explore how physicochemical characteristics and biological activity of partially chlorinated transformation products differ from the behavior of the parent PPCP. Furthermore, additional toxicological studies with transformation products are warranted, so as not to place too strong an emphasis on the results of *in vitro* toxicity assays; PPCPs may result in toxic endpoints other than estrogenic response that may only be observed through investigation of whole organism (*i.e.*, *in vivo*) toxicity.

Even for chemical oxidation strategies such as ozonation, which effectively degrades most PPCPs, mineralization (*i.e.*, the complete conversion into inorganic components such as CO_2) is not likely a realistic goal. Therefore, further identification and characterization of byproducts generated during wastewater treatment are needed. Early work in this area conducted by Huber *et al.*[88] examined the ozonation of 17α-ethinyl estradiol. Although small amounts of estrone and 17β-estradiol were observed, they concluded that most products exhibited chemical structures considerably altered from the parent, consistent with the loss in estrogenic activity measured in assays of the ozonation products.

More recent analysis of ozonation products seems to support a larger role of $^{\bullet}OH$ than may have originally been anticipated for PPCP treatment with ozone. Benner and Ternes[157] identified the products of metoprolol ozonation, primarily observing transformation products rich in aldehyde moieties and others indicative of hydroxylation reactions. Although they worked in model systems consisting of raw wastewater and secondary wastewater effluent spiked with metoprolol, these transformation products seem to suggest a significant role for $^{\bullet}OH$ during ozonation of PPCPs in wastewater matrices. Similarly, laboratory studies conducted by Radjenovic *et al.*[99] on the ozonation of antibiotics in both distilled water and secondary wastewater effluent revealed transformation products most consistent with $^{\bullet}OH$ reaction pathways, despite the relatively high affinity that many of the parent antibiotics exhibit toward ozone. Notably, two products of roxithromycin exhibited high refractoriness to ozonation. Both products maintained an intact tertiary amine moiety suggesting that antimicrobial activity may have been preserved after ozonation.

As pointed out by Snyder,[2] future research should not focus solely on the ecotoxicity of oxidation metabolites. Byproducts of ozonation include bromate (BrO_3^-) in bromide-containing waters, and organic products generated from the ozonation of DOM, which is present in wastewater at much higher concentrations than micropollutants. In a recent comparison of ozone to ozone-based AOPs, Wert *et al.*[158] found that ozone yielded a smaller amount of these byproducts relative to AOPs, which may be due to a lower degree of $^{\bullet}OH$ exposure during ozonation. Nevertheless, further research regarding the formation, ecotoxicological impacts and approaches for mitigating byproducts of wastewater ozonation and similar chemical oxidation strategies is warranted before such treatment measures can be routinely implemented.

C. Challenges of increased reliance on advanced treatment technologies

Oft-cited detriments of advanced wastewater treatment, including chemical oxidation and membrane technologies, are their high energy requirements and the associated ecological and economical costs. If advanced treatment of wastewater is deemed necessary, a careful evaluation of these costs should be performed when identifying an optimal treatment method. For example, energy consumption was recently evaluated at a full-scale plant using ozonation to degrade micropollutants in wastewater.[46] Results indicated that micropollutant concentrations could be drastically reduced with an energy demand from ozonation that amounted to only 12% of the total energy cost of a typical nutrient removal plant. This energy cost increased by approximately 30% if the production of pure oxygen for ozone generation was taken into account.

In a comparison of energy consumption associated with different advanced treatment methods, Rosenfeldt *et al.*[159] compared the energy use for different H_2O_2-based AOPs and ozone applied to surface and ground water. They found that at a low $^{\bullet}OH$ yield, ozone was the most efficient technology, whereas at higher yields the difference became negligible. Future direct comparisons of chemical oxidation-based treatment technologies should also include AOPs that can be operated with sunlight as the energy source and/or without the addition of H_2O_2, the use of which contributes greatly to operation costs. Two examples of AOPs that can use sunlight as the main energy source are homogeneous photo-Fenton processes using ferrous iron and H_2O_2, and heterogeneous solar photocatalysis with titanium dioxide. A life cycle analysis of these two AOPs coupled to biological treatment was evaluated in a noteworthy study by Munoz *et al.*,[160] taking into account the impact categories of global warming, ozone depletion, human toxicity, freshwater aquatic toxicity, photochemical ozone formation, acidification, eutrophication, energy consumption, and land use. Results showed that solar photo-Fenton has a lower environmental impact than solar heterogeneous photocatalysis for the treatment of industrial wastewater. The solar photo-Fenton process thus seems to be a more reasonable option if AOPs are to be employed.

In addition to those advanced methods already demonstrated as effective for PPCP removal, emerging oxidants, such as ferrate (Fe(VI)) and permanganate (Mn(VII)), could be scrutinized for their efficiency and environmental impact. Because these oxidants are not as commonly used as chlorine and ozone, PPCP removal by permanganate and ferrate has received less attention to date. However, it has been shown that they are capable of efficiently degrading endocrine disruptors and antimicrobials,[161,162] as well as carbamazepine.[163] Furthermore, their disinfection byproducts are considered benign[164] and the products of their reduction (*i.e.*, MnO_2 (s) and $Fe(OH)_3$(s)) can be exploited as coagulants to further contribute to the removal of PPCPs and EfOM (see Hu *et al.*[163] and references therein).

Similar considerations should also be applied for membrane technologies. Snyder *et al.*[71] emphasized that while membranes show great potential for enhancing wastewater quality, the benefits of membrane treatment must be weighed against possible detriments. Besides high energy requirements, these also include the removal and disposal of the concentrated brine produced during the process. Indeed, an economic analysis conducted by Jones *et al.*[165] suggests that the use of membrane filtration technologies for wastewater treatment may be ultimately both economically and ecologically undesirable as a result of the high energy demand.

V. Conclusions

Based upon available data, technological solutions currently exist that can be used to lower PPCP levels in wastewater effluent to sub-ng L^{-1} levels that push the limits of current analytical instrumentation. Experimental evidence clearly demonstrates that current limitations in conventional treatment practices can be overcome with advanced treatment strategies including chemical oxidation with ozone or the use of membrane technologies such as RO and NF, all of which improve considerably effluent quality when incorporated into wastewater treatment trains. We caution, however, that zero is neither a reasonable nor achievable treatment goal for PPCPs. Recent advances in engineered wastewater treatment must now be matched by ecotoxicological data that establish acceptable levels of PPCPs in wastewater effluent and regulations regarding thresholds for PPCP removal. Until these criteria are established, appropriate treatment technologies will be difficult to identify with certainty.

Ultimately, adequate removal of PPCPs from wastewater may require rethinking current paradigms in wastewater treatment and its associated infrastructure. For example, available data suggest that the use of passive treatment options often affords better PPCP removal than conventional treatment systems, while also providing the benefits of low energy input and minimal operation and maintenance costs. In populated areas, however, implementation of such systems may be limited by their large space requirement. Therefore, a model for future wastewater treatment infrastructure may involve decentralized systems that serve smaller population segments. Such systems could include primary or secondary treatment, followed by passive tertiary treatment with SAT, constructed wetlands or lagoons.

There is an increased reliance on reclaimed wastewater for applications including irrigation, habitat restoration, and potable reuse in water-stressed regions. Therefore, methods must be developed that better quantify the economical and ecological benefits of advanced treatment practices that enable such wastewater reuse strategies. Munoz *et al.*[166] used life cycle analysis to compare the toxicity implications of different water reuse strategies. They considered direct reuse of secondary effluent, as well as reuse of three tertiary treated effluents (RO, ozonation and H_2O_2/O_3). Their findings highlight the importance of non-regulated pollutants, including PPCPs, in the toxicity assessment of reclaimed water. Specifically, tertiary effluents exhibited lower ecotoxicity than secondary effluent, indicating tangible ecological benefits associated with advanced treatment. In the future, these benefits must be better quantified and weighed against more easily identifiable detriments commonly linked to advanced technologies, such as the energy demand associated with membrane technologies.

In all the scenarios outlined above, it is important to emphasize the need for more research involving actual wastewater matrices and full-scale WWTPs. This is particularly true for advanced treatment technologies such as membranes, ozonation, AOPs and activated carbon, for which current data are relatively limited. Because the efficiency of these strategies will be highly variable in response to the organic matter loads in wastewater, the current divide between water and wastewater PPCP research must be closed.

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